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Adenomyosis and infertility - underestimated challenge in reproductive medicine

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Abstract
Introduction: Adenomyosis is considered as a chronic gynecological condition increasingly observed among women of reproductive age. It remains underdiagnosed and frequently underestimated as a contributing factor in fertility disorders. Characterized by the presence of endometrial glands and stroma within the myometrium, adenomyosis causes progressive structural and functional uterine changes that may impair endometrial receptivity and disrupt implantation.
Aim of the study: This review aims to summarize current knowledge on the effects of adenomyosis on fertility. It focuses on the pathophysiological mechanisms involved, diagnostic tools, classification systems.. It explores the pathophysiological mechanisms that contribute to impaired reproductive outcomes, as well as available diagnostic methods that enable an effective identification of the condition.
Materials and methodology:The literature review includes articles from databases (PubMed), selected to their citation, using keywords “adenomyosis”, “infertility”
Conclusion: Adenomyosis is increasingly recognized as a potential contributing factor to female infertility. Anatomical and functional alterations within the uterus may impair embryo implantation and early pregnancy development. Current evidence highlights the importance of including adenomyosis in the diagnostic work-up and management of infertile patients. A deeper understanding of its underlying mechanisms may lead to more effective and individualized treatment strategies.

Keywords: adenomyosis; diagnosis; infertility; pregnancy; implantation failure; reproductive outcomes

Introduction

Adenomyosis is a condition that occurs in women of reproductive age, involving the infiltration of endometrial cells, which are usually found only in the uterine cavity, into the myometrium. This tissue contains glands and supporting elements (stroma), leading to changes in the structure of the uterus [1]. Thus, it may lead to symptoms like irregular periods, spotting between periods, painful menstruation, and difficulties getting pregnant, all of which can significantly impair their quality of life and have a long-term detrimental effect on their physical and mental health. The two different types, diffuse and localized, are commonly detected by transvaginal ultrasonography (USG) [2]. It is said that between 5 and 70% of people have adenomyosis, which suggests that more research should be necessary and justified [3].

The illness currently is recognized as a multidimensional disorder due to its diverse nature. Using non-surgical diagnostic methods, the number of diagnoses is increasing, especially among younger women. These results may be considered as the consequence of differences in the methods used to identify instances, the diversity of women in the study, or the diagnostic

criteria used. It should be mentioned that adenomyosis often co-occurs with other gynecological conditions, including uterine myomas and endometriosis [4].

Until recently adenomyosis was diagnosed mainly in premenopausal women, usually only after removal of the uterus and histopathological analysis. Nowadays, thanks to the development of modern imaging methods and the use of transvaginal ultrasound and magnetic resonance imaging (MRI) in diagnosis, it is possible to make the diagnosis at an earlier stage, already when it comes to women of reproductive age, without the need for surgery[5]. Despite the increasing access to modern diagnostic methods and the growing number of studies on adenomyosis, its impact on fertility still raises many questions and controversies. However, it is worth emphasizing that the early diagnosis and appropriately selected therapeutic management can significantly improve the prognosis of women planning a pregnancy, as well as significantly affect their quality of life.

Pathogenesis

Understanding the mechanisms underlying the development of adenomyosis remains a significant research challenge. Despite the passage of time the exact cause of this condition has not been clearly identified, so several theories have been proposed in order to explain its pathogenesis better[4]. Among the proposed concepts explaining the development of adenomyosis is the stem cell theory, which suggests that the condition may develop de novo as a result of metaplasia of endometrial progenitor cells or stem cells. These cells differentiate into endometrial foci that become embedded in the myometrium, especially in response to tissue damage. In contrast, according to other modern theories, adenomyosis develops as a result of invasive hypertrophy of the basal layer of the endometrium (endometrium basalis) deep into the myometrium. This process can result from structural abnormalities or the absence of a junctional zone (JZ), which promotes the penetration of endometrial cells into the myometrium [6]. Changes in the uterine junctional zone (JZ), such as increased thickness and impaired contractility, may hinder proper embryo transport and implantation. Additionally, reduced expression of progesterone receptors in the endometrium can limit the uterus's ability to create a receptive environment for implantation.

One of the postulated mechanisms underlying the development of adenomyosis is impaired endometrial receptivity, which results in impaired embryo implantation. Among the factors responsible for this condition are abnormal transformation of stroma cells during the cycle and

deregulation of adhesion molecules such as integrin β3, osteopontin and L-selectin. In addition, abnormal oxidative enzyme activity can lead to disruption of the endometrial microenvironment during the perimenopausal phase. At the molecular level, perturbations of signaling pathways such as PI3K/Akt, JAK2/STAT3 and Hedgehog, which are involved in the differentiation process of stromal cells, are crucial. Their dysfunction may limit the endometrium's ability to successfully implant the embryo, which is an important part of the pathogenesis of adenomyosis [7].

According to previous studies, mutations in the KRAS gene, which occur mainly in endometrial epithelial cells, may be important in the development of adenomyosis - and in a mechanism similar to that observed in endometriosis. These changes interfere with the normal function of the endometrium, causing excessive cell proliferation, reduced sensitivity to progesterone and disturbances in its cyclic remodeling. All this can lead to problems with embryo implantation [8].

Fibrotic mechanisms that aid in the structural remodeling of the uterine wall significantly contribute to the development of adenomyosis. Overproduction of collagen and alterations in the extracellular matrix composition lead to the progressive hardening of the uterine muscle as well as elevated presence and activation of myofibroblasts in adenomyotic foci is noted, which fosters the emergence of fibrogenic changes that disrupt the organ's normal function. This process is intricately linked to chronic inflammation, which can sustain and worsen fibrosis, leading to the appearance of clinical symptoms [9].

Classification of Adenomyosis

Adenomyosis, although often overlooked in discussions regarding to women's health, is gaining increasing attention in research related to fertility and reproductive disorders. Classifying this disease based on various criteria helps to better understand its impact on the body. Depending on where and how severe the uterine lesions are, adenomyosis can take different forms. This is important for proper diagnosis and further monitoring of the patient's condition.

The first classification of adenomyosis was proposed in 1972 by Bird and co-authors and was based solely on histological features of the disease, due to the lack of advanced imaging techniques available at the time[10].

Over the time, with the development of knowledge about the pathogenesis of the disease and advances in diagnostics, a more accurate approach to the classification of adenomyosis has become possible. This time, the localization of disease foci in the myometrium was taken into account. The concept that the inner and outer layers of the myometrium can be occupied independently of each other was also introduced, suggesting different mechanisms of disease development. On this basis, four main types of adenomyosis were distinguished (tab. 1).

Tab. 1. Classification of adenomyosis types based on lesion location within the myometrium [11]

Type of Adenomyosis	**Differentiation**
Internal (inner) adenomyosis	Involves lesions located in the layer adjacent to the endometrium.
Extrinsic (external) adenomyosis	Develops in the outer layers of the myometrium.
Parenchymal (intramuscular) form	Limited to the deeper layers of the myometrium.
Indeterminate type	Difficult to classify unequivocally.

The developed classification system, based on a detailed analysis of clinical and histological features, allows for more accurate tailoring of surgical treatment to the individual needs of patients with adenomyosis. This method enables precise determination of the type and characteristics of the condition, significantly facilitating the selection of the most effective therapeutic strategy [12].

The following groups are distinguished:

- **Diffuse adenomyosis**: is characterized by a thickening of the border zone (BZ) of the inner layer of the myometrium and extensive changes in the outer layer of the myometrium, with the presence of endometrial glands and stroma that spread into the myometrium.
- **Focal adenomyosis**: in this form, there are markedly limited masses of adenomyosis within the myometrium, as well as a cystic form of adenomyosis.
- **Polypoid adenomyosis:** including both typical and atypical forms.

➢ **Special types:** including adenomyosis of the endocervical type and retroperitoneal adenomyosis [13] .

Such a division is also important for predicting the results of therapy and selecting appropriate treatment methods.

Analyzing the classification proposals to date, it is noticeable that there are a variety of features that may be important in grouping cases. However, it should be emphasized that the classification should not only be precise, but also easy to apply in daily clinical practice, which will facilitate its implementation in working with patients.

Impact on fertility

Adenomyosis changes the structure and function of the uterus, therefore complicating conception. Still, one should be aware that its effect on fertility differs among various women. Adenomyosis does not in some cases, especially in asymptomatic people, prevent conception. Reproductive outcomes are comparable to those of healthy women. This suggests that the effect of adenomyosis on fertility is individual and does not always lead to infertility [14].Adenomyosis is often linked to fertility problems. This is mostly due to inflammation and changes it causes in the uterine lining. These issues can raise estrogen levels and cause stronger uterine contractions. As a result, it becomes harder for eggs and embryos to move and implant properly. Inflammation and scarring also weaken the endometrium's ability to support an embryo. This can reduce the chances of a successful pregnancy, especially during fertility treatment [15]. Studies show that women with adenomyosis may not only suffer from lower implantation and pregnancy rates but they are also more likely to miscarry. Some data suggest live birth rates can drop by up to 40% in these cases [16]. In addition, it is estimated that an isolated adenomyosis is diagnosed in about one in ten women with fertility problems, and its incidence increases when other conditions, such as endometriosis or uterine myomas, coexist [17].

Clinical manifestations and complications of adenomyosis

The variability of adenomyosis symptoms greatly affects the daily lives and functioning of patients. The symptoms can be extremely uncomfortable or almost undetectable. As the disease progresses, symptoms may worsen or change in nature, making diagnosis more difficult and choosing the best course of action more difficult. Adenomyosis also increases the risk of

pregnancy complications such as small for gestational age (SGA), high blood pressure, and preterm labor [15]. The illness lacks a definitive symptom that is simple to identify. It typically presents as painful periods, ongoing pelvic discomfort, abnormal bleeding, infertility issues, and pain during sexual activity. It is important to highlight, though, that nearly 30% of patients show no symptoms, complicating the diagnosis further [18].

One of the most common symptoms is abnormal uterine bleeding (AUB). To properly assess its cause, the PALM-COEIN classification is used to distinguish adenomyosis from other possible factors. According to this classification, adenomyosis is included among the structural causes, alongside uterine fibroids, polyps, and malignancies. Non-structural causes include coagulopathies, ovulatory disorders, endometrial abnormalities, iatrogenic factors, and undetermined etiology, among others. It is important to emphasize that the other causes can coexist with adenomyosis, further complicating diagnosis and requiring a comprehensive approach to each patient [19].

Like chronic endometritis, adenomyosis can have mild symptoms that are easy to dismiss. Spotting, irregular bleeding and pelvic pain are frequently disregarded. Adenomyosis is a benign condition, but it can have a big effect on reproductive health. This is why there is growing interest in its connections to gynecological problems, including difficulties with conception [20]. In the case of adenomyosis, the mechanisms underlying complaints such as painful menstruation and chronic pelvic pain remain not fully understood. Previous studies have increasingly emphasized the role of prostaglandins, which can exacerbate the symptoms of adenomyosis, particularly by affecting uterine contractions [21]. Adenomyosis often leads to menstrual disorders, which in more advanced cases may require surgical intervention, especially due to heavy bleeding. There are indications that the severity of bleeding is closely related to the progression of the disease and the depth of myometrial changes [1].

Diagnosis

Making an accurate diagnosis in clinical practice can be challenging, especially when symptoms are mild or unclear. Furthermore, overlapping or masking symptoms may obscure diagnosis in those with adenomyosis in conjunction with other uterine diseases including endometriosis or fibroids. Adenomyosis is diagnosed usually by a thorough examination combining clinical examination and advanced imaging technologies since there are no precise diagnostic criteria and the sensitivity of current imaging tools varies. The main techniques for

diagnosing adenomyosis are magnetic resonance imaging (MRI) and transvaginal ultrasonography (TVS).Common on MRI, low-signal subendometrial cysts with border zone (BZ) thickening of ≥12 mm show great sensitivity and specificity. However, such a value can also be found in an uterus without adenomyosis, which raises concerns about the use of rigid diagnostic thresholds[22]. TVS, especially with 3D-TVS technology, allows assessment of the structure of the myometrium and detection of characteristic changes such as hyperechoic lines, cysts and irregularities within the myometrium. Abnormalities within the border zone may indicate disease, but their evaluation depends on the experience of the examiner. Due to the limitations of both methods, their combined use is recommended to increase diagnostic accuracy [22]. Even though hysteroscopy is not the main technique for identifying adenomyosis, it can be a useful supplementary test. It allows for the detection of characteristic changes in the endometrium, such as excessive vascularization or submucosal cysts, which may indicate adenomyosis, through direct visualization of the uterine cavity.

Certain abnormalities such as an irregular arrangement of blood vessels in the endometrium may indicate the presence of the disease can be seen during the examination. They are insufficient, though, to provide a conclusive diagnosis. The ability to obtain tissue samples from the endometrium and surrounding uterine muscle during a hysteroscopy procedure is a significant benefit as it enables additional histopathological analysis. Consequently, it can be useful in the thorough diagnosis of adenomyosis even though it is not a definitive method [23,4]. Adenomyosis significantly affects fertility, particularly when it comes to in vitro fertilization (IVF) treatments, according to a study of 17 observational studies. According to the findings, women who have adenomyosis may have trouble becoming pregnant and may respond less well to infertility therapies. As a result, it has been highlighted that more accurate diagnosis criteria and a better comprehension of the processes relating adenomyosis to reproductive problems are required [24]. The use of imaging techniques in diagnosing adenomyosis is crucial, as each method has its specific features and limitations.Combining both approaches reduces the likelihood of diagnostic errors, particularly in patients with reproductive concerns, and helps to more accurately differentiate adenomyosis from other disorders including fibroids.

Treatment options

Despite the availability of various treatment options for adenomyosis, there is a lack of sufficient scientific evidence to conclusively determine their effectiveness. Therefore, further

research into the efficacy of these therapies and a deeper understanding of the disease's mechanisms are essential to improve therapeutic approaches for patients with adenomyosis.

1. Pharmacological methods

Non-steroidal anti-inflammatory drugs (NSAIDs) are often used to relieve symptoms of adenomyosis. These include painful periods, chronic pelvic pain, and irregular bleeding. The drugs help many patients by reducing pain and inflammation. However, about 20% of women with adenomyosis don't experience much relief, even though they're effective for menstrual pain. Women on hormone therapy or trying to get pregnant can also benefit from NSAIDs as they don't seem to affect fertility.

Also progesterone is used to treat adenomyosis, but it might not work well because there are fewer progesterone receptors in the affected tissues. Some improvement has been seen with higher doses of topical progesterone. However, there aren't enough studies to confirm how effective this treatment is for adenomyosis [25]. GnRH analogs are used to help improve implantation rates and clinical pregnancy outcomes. However, there has been no significant improvement in live birth rates or reduction in miscarriages [26].Aromatase inhibitors (IAs) work by blocking the aromatase P450 enzyme, which converts androgens into estrogens. Women with endometriosis, adenomyosis and uterine myomas experience abnormal activity of this enzyme, leading to excessive estrogen production and increased inflammation at the affected sites. The use of aromatase inhibitors to treat adenomyosis is a relatively new therapeutic approach [25,27]. Intrauterine levonorgestrel-releasing system (LNG-IUS) can be effective, especially when adenomyosis is confined to areas close to the uterine cavity. However, in intermediate or advanced cases involving the full thickness of the uterine wall, this method is unsuccessful [28].

2. Surgical Treatment

Hysterectomy continues to be a widely used and successful treatment for adenomyosis. It removes symptoms such as pain and excessive bleeding; however, unfortunately, the complete removal of the uterus causes permanent loss of fertility. Therefore, procedures that maintain the uterus, such as adenomyomectomy, are increasingly gaining popularity . With subtotal hysterectomy, retention of the cervix theoretically leaves a chance for continued fertility, although studies indicate that the likelihood of pregnancy after such a procedure is low. The choice of the surgical type will be based on the individual patient's preference, her wish to

remain fertile and assessment of the risk for complications, such as recurrence or difficulty in recovery [29, 30].

The kind of surgical procedure for addressing adenomyosis is determined by the position and severity of the disease areas. For focal lesions, laparoscopic intervention has been shown to be effective. In cases of more extensive disease, laparotomy is the favored approach, and occasionally, laparotomy aided by laparoscopy is employed as well. While laparotomy is more invasive, it provides higher accuracy in excising lesions, aiding in lowering the likelihood of disease recurrence and complications, like uterine rupture, that could arise in subsequent pregnancies [31]. The effectiveness of surgical treatment of adenomyosis in the context of fertility is still a topic of ongoing research. Nonetheless, available data suggest a potential benefit of surgery in improving reproductive outcomes. Although overall results remain inconclusive, numerous studies suggest that younger patients with a focal form of the disease may have better outcomes following surgery. Precisely determining the effect of these procedures on fertility is difficult, due to the variety of surgical techniques and the variability of symptoms. Therefore, further studies are needed to better understand how the chosen surgical approach affects the reproductive capacity of women with adenomyosis[32,33] .

It presents a unique challenges for women with adenomyosis, not only are they infertile, they also suffer severe pain, and have an elevated risk for serious obstetrical complications during the pregnancy, e.g. ureteral obstruction or bowel obstruction. Such treatment should only be performed in specialized medical facilities with the proper knowledge and resources [15].Uterine artery embolization, as a less invasive method, may be considered for patients with abnormal uterine bleeding who plan to preserve fertility. This technique effectively controls bleeding compared to hysterectomy and does not negatively impact fertility. The choice of this method is based on the individual needs of each patient and the specifics of the case, so treatment should be tailored to the particular situation and expectations [19].

Adenomyosis can be treated medically with hormonal therapies or surgically, including hysterectomy, adenomyomectomy, hysteroscopic resection, uterine artery embolization, or radiofrequency ablation. These techniques can help relieve symptoms and preserve fertility where it is possible.” The method chosen will depend on the particular situation of the patient and her fertility goals. As both methods have advantages and disadvantages, additional studies evaluating the long-term effects of these methods on reproductive outcomes are warranted.

3. Supportive Treatment

For patients preferring a conservative approach to treatment, radiofrequency ablation (RFA) may be an effective method for pain reduction in adenomyosis. RFA is faster and less invasive than other techniques (e.g., uterine artery embolization or high-intensity focused ultrasound (HIFU) therapy). While preliminary results suggest that the procedure is effective in alleviating symptoms such as menstrual pain, there are currently no established diagnostic standards to standardize treatment outcomes [34]. Although the effect of adenomyosis on fertility is not fully understood, research suggests that it may impede conception. In response, high-focused ultrasound therapy (HIFU) is emerging as a promising, minimally invasive treatment option. Proper patient selection is the key, as the method precisely removes lesions while preserving healthy uterine tissue. Thus, it speeds up the return to pregnancy planning, and its lower risk of complications makes HIFU a possible alternative to traditional surgery [35]. HIFU is becoming an increasingly promising treatment for adenomyosis, but further research is needed to fully confirm its efficacy, safety, and effect on fertility, so that it can be more widely introduced into clinical practice. Radiofrequency treatment is most promising in patients who are planning to get pregnant after the procedure, making it particularly ideal for fertility-preserving patients. All the techniques are safe and complications are rare [36].

Conclusions/ (summary)

Diagnosing and treating adenomyosis is a major challenge, especially for patients with fertility problems. The biological complexity of adenomyosis is due to the interaction of multiple mechanisms, of which molecular and endocrine disorders are particularly important. The disease's unclear and diverse clinical course emphasizes the need for more investigation. Deepening our knowledge of these processes may contribute to more precise diagnosis and more effective treatments, especially in patients trying for pregnancy.

Early detection of the condition is the key to developing an optimal treatment strategy. Although transvaginal ultrasonography (TVS) and magnetic resonance imaging (MRI) are the primary diagnostic tools for detecting adenomyosis, each of these methods has limitations that can affect the accuracy of diagnosis. As a result a more comprehensive diagnostic approach that combines different imaging techniques to improve the accuracy of diagnosis is increasingly being recommended. Treatment options for adenomyosis, such as surgeries and drug therapies (including NSAIDs, progestogens and GnRH analogs), still require further research. It is

necessary to improve our knowledge of their efficacy and long-term effects on fertility and reproductive outcomes. The effectiveness of some of these treatment methods in improving reproductive outcomes remains a subject of the debate, despite their partial success in reducing symptoms such as pain and irregular bleeding. Depending on the location and size of the lesions, surgical procedures such as laparoscopy and adenomyomectomy are used. However, their impact on fertility requires further assessment.

The degree of development of adenomyosis as well as the patient's personal reproductive goals largely determine the choice of appropriate treatment. Although this applies to only a small percentage of patients, hormonal therapy or the use of a levonorgestrel-releasing intrauterine device (LNG-IUS) may be beneficial in certain situations. Surgical procedures, such as adenomyomectomy or hysterectomy, may be necessary in cases of moderate to severe adenomyosis. Although further research is needed to fully understand their effectiveness, less invasive treatment methods, such as uterine artery embolization, radiofrequency ablation, or high-intensity focused ultrasound (HIFU), offer hope for women trying to preserve their fertility.

To get the best results, treatment should be customized to the patient's unique needs and reproductive objectives. In order to give patients better, more individualized care, it is also essential to develop consistent diagnostic and therapeutic approaches.To completely comprehend the mechanisms underlying adenomyosis and to create efficient treatment plans, longer-term research is still required.

Modern treatment of adenomyosis should not only consider medical issues but also emotional and social aspects if it is to provide patients with comprehensive care tailored to their unique needs. At the same time, the creation of uniform diagnostic and therapeutic techniques is essential to provide patients with better, more personalized therapy, especially for those who wish to preserve their fertility. To fully understand the processes underlying adenomyosis and to create effective treatment plans, long-term studies are still needed.

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